ABCdb: an ABC Transporter Database

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Abstract

We present the first release of a database devoted to the ATP-binding cassette (ABC) protein domains (ABCdb). The ABC proteins are involved in a wide variety of physiological processes in Archea, Bacteria and Eucaryota where they are encoded by large families of paralogous genes. The majority of ABC domains energize the transport of compounds across the membranes. In bacteria, ABC transporters are involved in the uptake of a wide range of molecules and in mechanisms of virulence and antibiotic resistance. In eukaryotes, most of them are involved in drug resistance and in human cells, many are associated with diseases. Sequence analysis reveals that members of the ABC superfamily can be organized into sub-families and suggests that they have diverged from common ancestral forms. In this release, ABCdb includes the inventory and assembly of the ABC transporter systems of completely sequenced genomes. In addition to the protein entries, the database comprises information on functional domains, sequence motifs, predicted trans-membrane segments, and signal peptides. It also includes a classification in sub-families of the ABC systems as well as a classification of the different partners of the systems. Evolutionary trees and specific sequence patterns are provided for each sub-family. The database is endowed with a powerful query system and it was interfaced with blastP2 program for similarity searches. ABCdb has been developed in the ACeDB format, a database system developed by Jean Thierry-Mieg and Richard Durbin. ABCdb can be accessed via the World Wide Web (http://ir2lcb.cnrs-mrs.fr/ABCdb/).

Introduction

ABC transporter systems, also termed traffic ATPases, are found in the three major kingdoms of life (Prokaryota, Archea and Eucaryota, reviewed by Higgins, 1992). The majority mediate the active uptake or efflux of specific molecules across the biological membranes. They handle a wide variety of compounds, which differ in nature and size (i.e. oligosaccharides, amino acids, peptides, antibiotics, metallic cations... Ames, 1986). A typical ABC transporter is composed of two Membrane Spanning Domains (MSD) and two Nucleotide Binding Domains (NBD). The import systems are associated with a Solute Binding Protein (SBP). The MSDs constitute the membrane channel and the NBDs, in close interaction with the MSDs, energize the transport via ATP hydrolysis. The SBPs are soluble and periplasmic in Gram negative bacteria and anchored to the membrane in Gram positive bacteria. The SBPs confer specificity for compounds to the transporter. In bacteria, ABC systems are generally encoded by neighboring genes. In eukaryotes, they usually correspond to a single amino acid chain and only export systems have been described. Many of them are involved in multi-drug resistance or genetic diseases (for review, see Holland and Blight, 1999).

Recently, the question of the inventory of the ABC transporters in yeast and bacterial complete sequenced genomes has been addressed by several authors (Taglicht and Michaelis, 1997; Decottignies and Goffeau, 1997; Poulis et al., 1998a, 1998b; Linton and Higgins, 1998; Quentin et al., 1999; Dassa et al., 1999; Tomii and Kanehisa, 1998), and these studies revealed that ABC systems can be arranged in a comprehensive classification that is well correlated with compound specificity of transport. Comparative analyses of repertory of ABC transporters between genomes suggest that ABC transporters derive from successive waves of duplications and that the ancestral ABC transporter may have arisen early in evolution, before the differentiation of prokaryotes and eukaryotes, in the last common universal ancestor (Tomii and Kanehisa, 1998 and Saurin et al., 1999). These observations motivate the development of a database dedicated to ABC transporters. Such a database should be useful to predict the compound specificity of hypothetical transporters obtained through systematic sequencing, but should be also relevant for studies of multi-drug resistance of eukaryotic cells, virulence and antibiotic resistance of prokaryotes. This database will constitute a very good platform for further evolutionary and structure-function relationship studies.

Source of Data

The primary data are retrieved from the Genome page of the NCBI server (http://www3.ncbi.nlm.nih.gov/Entrez/Genome/org.html) as GenBank flat files. The files are reformatted with perl programs before their importation in ABCdb. In the public version, only peptides and information on proteins related to ABC transporters are available. As far as possible, the protein names are those given in the GenBank entries to allow cross-linking between NCBI and ABCdb. The strategies we have adopted for automatic partner recognition is summarized on our WEB site (http://ir2lcb.cnrs-mrs.fr/ABCdb/) and will be published elsewhere.

Database Design

We administer our data with the ACeDB system developed by Thierry-Mieg and Durbin (ACeDB is an acronym for ACaenorhabdis elegans DataBase). ACeDB was created...
for managing the nematode genome project and in this context the system and the database have the same name. In the ACeDB system the data are stored in objects, which fall in a number of classes and each class is defined by a model. In the implementation of the ABCdb, we created some new classes “Assembly”, “Classif”, “Sub-family”, “Pattern” and “Profile”. The class Assembly is used to describe multi-protein systems such as ABC transporters (Figure 1). Its model includes tags for the origin, the (putative) function of the system and for the protein partners involved in the multi-protein assembly. For ABC systems, the partners are decomposed as functional domains (NBD, MSD, and SBP) and a tag (Domain_Organization) is used to define the contribution of each domain in the system. As illustration, the ABC transporter of the arabinose uptake is given Figure 1. Since the multi-protein assembly is the functional unit, we associated the functional classification of the ABC transporters to the “Assembly” class. The functional classification is modeled by a class “Classif” that is fairly simple in this primary version of the database. The purpose of this class is to collect and summarize the experimental data available on the systems. This work cannot be done automatically and will be achieved progressively by manual contributions of human experts.

On the other hand, the proteins and proteins domains can be automatically classified in sub-families with computer tools based on combinations of profiles (the pattern). Therefore, we design three new classes corresponding to the sub-families, the patterns and the profiles. Each sub-family is defined by a pattern, which includes one or several profile(s) computed by the MEME program (Bailey and Elkan, 1994).

The model of the “Protein” class has been fairly simplified regarding the ACeDB distribution package but few lines have been added for the creation of links with the new classes. The public version of the database does not include DNA sequence data but the coordinates of the genes on the chromosome are included in the “Protein” class. On the WEB version, hyperlinks to the NCBI genomic display are automatically generated.

We used the recent development of dendrogram tree display due to Richard Bruskiewich (Sanger Centre) to represent trees. Two kinds of trees are available in the database: a tree reflecting the taxonomy of the genomes as it can be found on the NCBI server, and evolutionary trees obtained on the proteins of each sub-family. Each evolutionary tree is computed with the NJ method (Saitou and Nei, 1987) from a distance matrix based on a multiple alignment obtained with ClustalW (Thompson et al., 1994). However, such trees, automatically generated, should be considered only as indicative (Figure 2). One can navigate along the tree and display the information associated with the nodes or the leaves with the mouse button. This is a simple way to browse through the information contained in the database.

Relationships between the classes of the database core are summarized in Figure 3. The Protein class has a central position with links to all the other facets of the ABCdb: the systems (Assembly and Classif), the motifs (Profile and Pattern), the sub-families (Sub-family and Family), the genomes (Species and Taxon), and the trees (Tree and Treenode). Since each pattern is diagnostic of a sub-family, there is a direct link between both classes. The link to Species is added in Assembly model to facilitate the cross-queries between these classes.
Data Query

The simplest way to explore the database is to follow the links present in the objects, or to search for objects in a given class or in all classes (See Figure 4, “Simple Search” option). The search can be restricted by a sub-string included in the name of the objects to retrieve. The result appears as a list of object names and each object can be displayed with a mouse “double-click” on its name.

The ACeDB system also includes a powerful query language (See Figure 4, “Ace Query” option). Since, the queries are applied to tags and data contained in objects, the knowledge of the class models is required. Therefore, the first query could be to list the database models (enter the query: “find model”). A query is composed of commands, operators and patterns. The find command is used to retrieve the list of objects belonging to a given class and matching the supplied pattern. Composite queries can be achieved by chaining a series of simple queries separated by semicolons. Each query is applied to the list of objects retrieved by the previous one. The follow command can be used to retrieve objects attached to a specified tag present in a list of objects selected by a find command.

As examples of find command, the simple queries “find Protein Ecol*” lists all proteins with names that begin with Ecol* and “find Protein Membrane_segment < 5 OR Membrane_segment > 8” gives all proteins containing less than 5 TMs or more than 8 TMs. As example of complex queries using the follow command, “find Species Lineage = Archaea; follow Assembly; follow Functional_Classification” gives the list of ABC system sub-families present in Archaea, and “find Assembly Domain_Organization = “SBP”; follow Partners; Domain_Structure =“MSD” AND NOT Profil_homol =EAA” retrieves the membrane proteins of uptake systems that do not contain the EAA motif. Detailed instructions and other queries can be found at http://ir2lcb.cnrs-mrs.fr/ABCdb/.

An another powerful tool is the “TableMaker”, which does not retrieve lists of objects but builds complex tables from data gathered in the same or different classes. Each column in the table is the result of a query. One application of the “TableMaker” is to tabulate the partners of each ABC system according to a criterion such as genome origin or sub-family classification. This tool will not be further described, as it is not yet available in the web version of the database, but example of tables are provided on our web site.
Protein Analysis Tools

We implemented a blastP2 form on our web server (Figure 5). The user query is compared to all proteins of ABCdb and html links to the protein objects and sub-families are added in the output in order to facilitate the classification and comparison of the query with ABCdb entries.

ACeDB Software and Data Access

The public version of ABCdb is available at the following address, http://ir2lcb.cnrs-mrs.fr/ABCdb/. Comments, suggestions and corrections can be addressed to quentin@ir2lcb.cnrs-mrs.fr. Users of ABCdb are politely asked to cite this article within scientific publications related to its use.

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References